DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

Rec'd 9/7/77

Honorable Joseph D. Early
House of Representatives
Washington, D.C. 20515

SEP 09 1977

Dear Mr. Early:

Thank you for your letter of August 2, 1977, on behalf of Mr. James G. Affleck, chairman and president of American Cyanamid Company, concerning tetracycline antibiotics.

Mr. Affleck's statement that the Commissioner of Food and Drugs has announced the intention of banning the use of tetracycline antibiotics in livestock and poultry feeds is incorrect as are a number of other statements in his letter. The American Cyanamid Company's widescale effort to discredit the Commissioner's announced intentions has utilized numerous inaccurate and misleading statements. We appreciate the opportunity to respond to the issues addressed in Mr. Affleck's letter.

The announced intentions of the Commissioner to restrict certain uses of chlortetracycline and oxytetracycline in animal feed are expected to be published as proposals in the Federal Register later this summer. No unilateral action will be taken by the Food and Drug Administration. The proposals, offering opportunity for public comment, will address in detail the scientific basis upon which action in the interest of the public health should be initialed. Thoughtful analysis of the contents of the proposals will be welcomed from all public segments including the scientific, agricultural and agri-business communities.

The proposals concerning tetracycline antibiotic drugs will be to withdraw subtherapeutic uses for which there are alternative drugs being marketed. Therapeutic uses of the tetracyclines in animal feeds and nontherapeutic uses for which there are no alternative drugs available will be retained for use by the livestock industry. Effective alternative drugs available for the uses of tetracyclines include bacitracin (zinc and methylene disalicylate), erythromycin, bambermycin, carbadox, oleandomycin, tylosin, poloxalene, sulfaquinoxaline, hygromycin B, sulfadimethaxine-ormetoprim, arsanilic acid, roxarsone, carbarsone, arsanilate sodium, lincomycin, monensin, virginiamycin. Some of these alternative drugs could become subject to additional restrictions in the future, but many of them have been shown to be safe under the criteria under which the tetracycline drugs have failed to meet.

The Agency discussed the use of antibiotics in animal feeds with the National Advisory Food and Drug Committee (NAFDC) in June 1975. The NAFDC requested that it assist in the policy-making decisions on the issue. Since the NAFDC is rather broadly based in membership, representing several professional disciplines and consumers (list of members enclosed),

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the full Committee recommended that a Subcommittee on Antibiotics in Animal Feeds be formed with expert consultants to consider more definitively the scientific, technical and public health issues. The members appointed to the Subcommittee were Dr. J. E. Mosier, Department of Surgery and Medicine, College of Veterinary Medicine, Kansas State University; Dr. Nelson Fernandez, Department of Biochemistry and Nutrition, School of Medicine, University of Puerto Rico; and Ms. Camille Haney, Consumer Concepts Management Consultants. They were assisted in their deliberations by four recognized expert consultants in the area of concern: Dr. George Poppensiek, College of Veterinary Medicine, Cornell University; Dr. William Flatt, Director, Agriculture Experimental Station, University of Georgia; Dr. Edward Hook, Jr., Department of Medicine, University of Virginia School of Medicine; and Dr. Stanley Falkow, Department of Microbiology, University of Washington. The actual experts in the deliberations on the issue, therefore, were the members of the Subcommittee and their consultants.

The Subcommittee issued its final report to the parent NAFDC after intensive deliberations on January 24, 1977. The report contained rather specific recommendations about the use of penicillin and the tetracyclines. Enclosed is a copy of Commissioner Kennedy's April 15, 1977 statement to the NAFDC which summarized the Subcommittee's pertinent recommendations as well as fully explaining the rationale for adopting its recommendations.

As has been indicated, the parent NAFDC accepted the recommendations of the Subcommittee concerning penicillin. However, the NAFDC did not agree with the Subcommittee's recommendation concerning the tetracyclines recommending instead that no changes be made in the present uses for products containing tetracyclines. This position was to be reevaluated with three years, and reports of any new information were to be discussed with the NAFDC every six months.

We carefully considered the recommendations of the NAFDC, the Subcommittee, and our Bureau of Veterinary Medicine. We intend to implement the basic recommendations of the Subcommittee, which along with its expert consultants, presented what we believe to be the most considered and indepth recommendatior We recognize that this is contrary to the recommendation of the full NAFDC, but the public health expertise in the issue clearly was in the Subcommittee with its consultants and the technical staff in our Bureau of Veterinary Medicine. Consequently, the contention by Mr. Affleck that the Agency rejected the recommendation of the NAFDC is technically correct but misleading.

The Commissioner has stated that:

> "Although we can point to no specific instance in which human disease is more difficult to treat because drug resistance has arisen from an animal source, it is likely that such

> problems could have gone unnoticed. The theoretical possibility that drug-resistant pathogens can be produced by antibiotic selection has become a real threat with the emergence of human diseases (typhoid and childhood meningitis) caused by ampicillin- and chloramphenicol-resistant Salmonella and Haemophilus. The point is that known routes of transfer exist by which antibiotic use in animals can contribute to such threats."

Dr. Kennedy's statement is based upon a number of well-documented facts from the recent scientific literature. Many studies have shown that the subtherapeutic use of antibiotics in animal feed leads to an increase in transferable drug resistance in E. coli in comparison to nonmedicated controls (Williams et al., 1977; Bulling and Stephens, 1972; Finlayson and Barnum, 1973; Levy et al., 1976; Smith and Tucker, 1975; Mercer et al., 1971; Van den Heeven, 1972; and Loken, 1971).

Recent studies have shown passage between animal and man of easily recognized strains of E. coli or Salmonella with specially marked R-plasmids (Levy et al., 1976; Hirsch and Wiger, 1976; American Cyanamid submission to FDA, April 1974; Linton et al., 1977; Cooke et al., 1970; and Siegel, 1976). R-plasmids are small transferable circles of DNA which occur outside the bacterial chromosome and carry genes specifying for antibiotic resistances. Other studies have demonstrated the close relationship or identity of animal and human E. coli, based upon serological studies (Hartley et al., 1975) and new techniques of molecular biology which show closeness of relationship or nucleotide sequences in plasmids from man and animals (e.g., DNA/DNA hybridization, heteroduplex analysis) (Anderson, Humphreys and Willshaw, 1975).

A number of studies have shown that humans in contact with animals receiving medicated feed have a higher incidence of drug-resistant organisms in their flora than do control populations. In addition, as stated earlier, the direct spread of resistant organisms from animals to man has been demonstrated using specially marked R-plasmids.

Studies have shown similarity between bacterial plasmids from animals and man based upon plasmid compatibility, i.e., the ability of two plasmids to coexist in a bacterial cell (Datta, FDA Contract 73-7210). Epidemiological studies have shown that the same phage types of S. typhimurium and the same classes of plasmids are present in both man and animal bearing resistance to a larger number of antibiotic resistances. The same types of Salmonella typhi plasmids and antibiotic resistances were also found in man during this worldwide survey (Anderson, 1975). Furthermore, the ampicillin resistance gene sequences from animal and human E. coli have shown to be similar to those from Haemophilus influenzae and Neisseria gonorrheae (Elwell et al., 1975; and Elwell et al., 1977).

Antibiotic resistant E. coli, favored by use of antibiotics in animal feed may transfer their plasmids to nonresistant Salmonellae in animals, which may be acquired by man (Anderson, 1969). The antibiotic-resistant E. coli may themselves be accquired by man and transfered to nonresistant Salmonella organisms acquired from animals and causing food poisoning. Boston patients who were given antibiotic therapy developed drug-resistant Salmonellae and excreted the organisms longer than nontreated patients (Aserkoff and Bennett, 1969).

There is some evidence that the addition of certain antibiotics to animal feeds does increase production efficiency and probably helps prevent infection. It is our belief that these results are obtained at great risks to the public health, and that the laws regarding safety of animal drugs require us to act to restrict that risk.

We are preparing an economic analysis of our proposed actions which will be available at the time our proposals are published in the Federal Register.

We appreciate the opportunity to respond to your inquiry. Please advise us if we can be of any further assistance.

Sincerely yours,

Robert C. Wetherell, Jr., Director
Office of Legislative Services

4 Enclosures

cc: HFC-20(2)(w/cy inc.)